Complete Summary

GUIDELINE TITLE

American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma.

BIBLIOGRAPHIC SOURCE(S)

American Society of Clinical Oncology Bisphosphonates Expert Panel. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol 2002 Sep 1;20(17):1-19. [72 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Multiple myeloma
- Lytic bone disease

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To determine clinical practice guidelines for the use of bisphosphonates in the prevention and treatment of lytic bone disease in multiple myeloma and to determine their respective role relative to other conventional therapies for this condition

TARGET POPULATION

Multiple myeloma patients with lytic bone disease

INTERVENTIONS AND PRACTICES CONSIDERED

1. Bisphosphonates, such as pamidronate (Aredia) and zoledronic acid (Zometa), for prevention and treatment of lytic bone disease in multiple myeloma

   Note: Although worldwide seven bisphosphonates are available for various conditions, only pamidronate intravenous and zoledronic acid are currently approved by the United States Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma and other metastatic disease. In Canada, both pamidronate and clodronate are approved for use in patients with metastatic bone disease.

2. Intermittent evaluation (every 3-6 months) for the presence of albuminuria and azotemia

MAJOR OUTCOMES CONSIDERED

Major Outcomes

- Length of survival (disease-free or overall)
- Quality of life
- Short- and long-term toxicities of treatment
- Cost-effectiveness

Intermediate Outcomes

- Biomarkers
- Radiographic criteria for bony response or progression
- Bone mineral density
- Skeletal-related complications/morbidity (e.g., fractures, spinal cord compression, hypercalcemia, and pain)
- Number of fractures per person-year
- Progression of osteolytic lesions per person-year
- Composite end point of skeletal related events (SREs) divided by the time on trial for each patient
- Time to first skeletal related event

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pertinent information from the published literature was retrieved and reviewed for the creation of this guideline. Computerized literature searches of MEDLINE (National Library of Medicine, Bethesda, MD) were performed through January 2002. Abstracts presented at American Society of Clinical Oncology (ASCO) annual meetings were also included. Key words/phrases included in the literature search were: multiple myeloma, diphosphonates/bisphosphonates, bone neoplasms, efficacy, surgery, radiotherapy, pain management/palliative care, spinal cord compression, and pathologic fractures. Limits included clinical trials, English language, and human studies.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Type of Evidence

Level I: Evidence obtained from meta-analysis of multiple, well-designed controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).

Level II: Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).

Level III: Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series.

Level IV: Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.

Level V: Evidence from case reports and clinical examples.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Values for levels of evidence and grade of recommendations were assigned by expert reviewers and approved by the panel. Expert consensus was used if there were insufficient published data. The panel addressed which patients to treat and when to treat them in the course of their disease. Additionally, specific drug delivery issues, duration of therapy, initiation of treatment and management of treatment of lytic bone disease was reviewed and compared with other forms of therapy for lytic bone lesions. Finally, the panel discussed patient and physician expectations associated with this therapy for bone metastases, as well as public policy implications related to the use of bisphosphonates.

The guideline was circulated in draft form, and all members of the Panel had an opportunity to comment on the levels of evidence, as well as the systematic grading of the data supporting each recommendation.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade for Recommendation

Grade A: There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.

Grade B: There is evidence of types II, III, or IV and findings are generally consistent.

Grade C: There is evidence of types II, III, or IV but findings are inconsistent.

Grade D: There is little or no systematic empirical evidence.

COST ANALYSIS

Commentary: Public Policy and Cost-Utility Implications

The widespread use of bisphosphonates will have a major impact on drug budgets within capitated or nationalized health care systems. The cost consequences and patient expectation of benefit will vary depending on (1) the phase of myeloma

when bisphosphonates are initiated, e.g., solitary plasmacytoma, stage I, II, or III, asymptomatic lytic disease, symptomatic lytic disease, or osteopenia only; (2) the specific bisphosphonate used; and (3) how the bisphosphonate is delivered.

The time to initiate bisphosphonates is a critical issue with an incomplete database. The available clinical trials show a clear benefit from intravenous pamidronate or zoledronic acid administered intravenously every 3 to 4 weeks in myeloma patients with radiographic evidence of lytic bone disease.

Preventing feared complications such as fracture and bone pain should lead to measurable life indicators. In the pamidronate trial, if patients had bone pain at entry, a consistent improvement in subsequent pain control was found. For many patients, this drug was associated with better maintenance of Eastern Oncology Cooperative Group (ECOG) criteria or World Health Organization performance status over time. Therefore, the costs and modest inconvenience of intravenous bisphosphonates are important concerns that must be balanced against these benefits.

Cost-benefit analyses could compare the various bisphosphonates to each other and/or no treatment. Two retrospective cost-effectiveness analyses using data from two of the clodronate-placebo trials found that reducing hospitalization costs associated with skeletal-related events (SREs) was the critical variable. Although these studies were incomplete in many key elements, each projected an increase in overall treatments of 22% and 17% with clodronate. No cost-effectiveness studies of either pamidronate or zoledronic acid versus placebo or each other are available. Because these agents are each more effective than clodronate but substantially more expensive, it is unlikely that overall costs will be reduced.

With the recent approval of zoledronic acid, in the United States the decision facing most cancer providers will be whether to switch from pamidronate to zoledronic acid. In 2001, pamidronate became a generic drug with at least two different companies (Bedford Pharmaceuticals, Bedford, OH and American Pharmaceutical Partners, Los Angeles, CA) distributing a generic form that is typically hundreds of dollars lower in price. However, pamidronate´s longer infusion time compared with zoledronic acid (2 hours versus 15 minutes) is associated with an opportunity cost to the patient (time), the cancer location (use of infusion chair), and extra staff time (reflected in common procedural terminology codes). A time and motion study at three outpatient chemotherapy infusion sites participating in the zoledronic acid versus pamidronate clinical trial found an average visit time for zoledronic acid patients was 1 hour, 6 minutes, compared with 2 hours, 52 minutes for pamidronate patients. From the infusion center perspective, the opportunity benefit for zoledronic acid was an average increase in 1.8 chairs per day available for other patients.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

An external review by individuals not directly involved in development of the guideline assessed the clarity, utility, and completeness of the document. The content of the guideline and the manuscript were reviewed and approved by the American Society of Clinical Oncology (ASCO) Health Services Research Committee (HSRC) and by the American Society of Clinical Oncology Board of Directors before dissemination.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I-V) and strengths of recommendation (A-D) are defined at the end of the Major Recommendation field.

Lytic Disease on Plain Radiographs

For multiple myeloma patients who have on plain radiograph(s), lytic destruction of bone, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended.

(Level of evidence: II; Grade of recommendation: B)

Monitoring

In patients with pre-existing renal disease and a serum creatinine less than 265 micromol/L or less than 3.0 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates in patients with worse function has been minimally assessed.

Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided.

The Panel recommends intermittent evaluation (every 3 to 6 months) of all patients receiving chronic pamidronate or zoledronic acid therapy for the presence of albuminuria and azotemia. In patients experiencing unexplained albuminuria (defined as more than 500 mg/24 hours of urinary albumin) or azotemia (defined as an increase of $\geq$0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL among patients with normal baseline serum creatinine levels), discontinuation of the drug is warranted until the renal problems are resolved. These patients should be reassessed every 3 to 4 weeks (with a 24-hour urine collection for total protein and urine protein electropheresis) and pamidronate reinstituted over a longer infusion time ($\geq$2 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline.

(Level of evidence: V; Grade of recommendation: D)

Duration of Therapy

The Panel suggests that, once initiated, intravenous pamidronate or zoledronic acid be continued until there is evidence of a substantial decline in a patient's

general performance status. The Panel stresses that clinical judgment must guide at what point the potential palliative benefits of pamidronate or zoledronic acid are less than the inconvenience of receiving this intravenously administered drug. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.

(Level of evidence: None available [N/A]; Grade of recommendation: Panel Consensus)

Myeloma Patients With Osteopenia Based on Normal Plain Radiograph or Bone Mineral Density Measurements

It is reasonable to start intravenous bisphosphonates in multiple myeloma with osteopenia but no radiographic evidence of lytic bone disease. Note: patients with nonlytic lesions have been included in selected trials but have not been the primary focus of the trial and never of sufficient number to be separately analyzed.

(Level of evidence: Insufficient data [N/A]; Grade of recommendation: Panel Consensus)

Patients With Solitary Plasmacytoma or Smoldering or Indolent Myeloma Without Documented Lytic Bone Disease

Starting bisphosphonates for patients with solitary plasmacytoma (Frassica et al., 1989) or smoldering or indolent myeloma (Alexanian, 1980; Kyle, 1978) is not suggested.

(Level of evidence: N/A; Grade of recommendation: Panel Consensus)

Patients With Monoclonal Gammopathy of Undetermined Significance (MGUS)

Starting bisphosphonates for patients with monoclonal gammopathy of undetermined significance (MGUS) (Kyle, 1978) is not suggested.

(Level of evidence: N/A; Grade of recommendation: Panel Consensus)

Biochemical Markers

The use of biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care.

(Level of evidence: III; Grade of recommendation: C)

Role in Pain Control Secondary to Bony Involvement

Intravenous pamidronate or zoledronic acid are recommended for patients with pain due to osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures or impending fractures.

(Level of evidence: II; Grade of recommendation: B)

Definitions:

Type of Evidence

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Grade C: There is evidence of types II, III, or IV but findings are inconsistent.

Grade D: There is little or no systematic empirical evidence.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations"). Where evidence was lacking, recommendations were made by consensus of the group.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Reported benefits include reduction of skeletal complications, including vertebral fractures.

POTENTIAL HARMS

Reported complications include:

- Renal toxicity, including albuminuria and azotemia
- Transient myalgias, arthralgias, and flu-like symptoms with fever
- Mild infusion site reactions
- New or worsening anemia
- Uveitis and other ocular manifestations, including iritis

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The recommendations for use of bisphosphonates specifically do not address the use of bisphosphonates as therapy for hypercalcemia in multiple myeloma or other malignancies.
- Guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Accordingly, the American Society of Clinical Oncology (ASCO) considers adherence to the guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient´s individual circumstances. The guidelines cannot be assumed to apply to interventions performed in clinical trials, which are designed to test innovative and novel therapies. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Society of Clinical Oncology Bisphosphonates Expert Panel. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol 2002 Sep 1;20(17):1-19. [72 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Sep 1

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

GUIDELINE COMMITTEE

American Society of Clinical Oncology Bisphosphonates Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Expert Panel Members: James R. Berenson, MD (Co-Chair), Cedars-Sinai Medical Center and UCLA; Bruce E. Hillner, MD (Co-Chair), Medical College of Virginia; Kathy S. Albain, MD, Loyola University Medical Center; Ken Anderson, MD, Dana-Farber Cancer Institute; J. Sybil Bierman, MD, University of Michigan; Brent A. Blumenstein, PhD, American College of Surgeons; Linda Bosserman, MD, Wilshire Oncology Medical Group; Rowan T. Chlebowski, MD, PhD, Harbor UCLA Medical Center; Donna J. Glover, MD, CCC Medical Group; Robert C. Hermann, MD, Northwest Georgia Oncology Centers; James N. Ingle, MD, Mayo Clinic; Nora A. Janjan, MD, M.D. Anderson Cancer Center; Robert A. Kyle, MD, Mayo Clinic; Allan Lipton, MD, The Milton S. Hershey Medical Center; Jacinta Meharchand, MD, Ontario Cancer Institute/Princess Margaret; Patricia Twilde, Patient Representative; Gary C. Yee, PharmD, University of Nebraska Medical Center

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Expert Panel complied with American Society of Clinical Oncology (ASCO) policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. No conflicts were identified that required any individual's role to be limited.

ASCO Bisphosphonates Expert Panel

James R. Berenson, MD, Co-Chair, Cedars-Sinai Medical Center and UCLA, Los Angeles, CA, Hematology Oncology
A consultant within the past 2 years for Novartis; received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis; received research funding from Novartis.

Bruce E. Hillner, MD, Co-Chair, Medical College of Virginia
Richmond, VA, Health Services Research
No conflicts noted.

Kathy S. Albain, MD, Loyola University Medical Center
Maywood, IL, Medical Oncology
No conflicts noted.

Ken Anderson, MD, Dana-Farber Cancer Institute
Boston, MA, Hematology Oncology
Received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis.

J. Sybil Bierman, MD, University of Michigan, Ann Arbor, MI
Surgery
A consultant within the past 2 years for Novartis.

Brent A. Blumenstein, PhD, American College of Surgeons
Chicago, IL, BioStatistics
No conflicts noted.

Linda Bosserman, MD, Wilshire Oncology Medical Group, Pomona, CA, Medical Oncology
A consultant within the past 2 years for Novartis; received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis; received research funding from Novartis.

Rowan T. Chlebowski, MD, PhD, Harbor UCLA Medical Center,Torrance, CA, Medical Oncology
A consultant within the past 2 years for AstaZeneca; received honoraria directly in

excess of $2,000 per year or $5,000 over a 3-year period from Novartis, AstaZeneca, and Pharmacia

Donna J. Glover, MD, CCC Medical Group, Philadelphia, PA
Medical Oncology
No conflicts noted.

Robert C. Hermann, MD, Northwest Georgia Oncology Centers, Marietta, GA, Medical Oncology
No conflicts noted.

James N. Ingle, MD, Mayo Clinic, Rochester, MN
Medical Oncology
A consultant within the past 2 years for Novartis; received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis; received research funding from AstraZeneca; and a member on the Board of Director´s or advisory committee of Pharmacia.

Nora A. Janjan, MD, M.D. Anderson Cancer Center, Houston, TX, Radiation Oncology
No conflicts noted.

Robert A. Kyle, MD, Mayo Clinic, Rochester, MN
Hematology
Received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis, Celgene, Schering, or OrthoBio/Tech.

Allan Lipton, MD, The Milton S. Hershey Medical Center Hershey, PA, Medical Oncology
Has ownership interests in Novartis; Received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis.

Jacinta Meharchand, MD, Ontario Cancer Institute/Princess Margaret, Toronto, Canada, Medical Oncology
No conflicts noted.

Patricia Twilde, Annandale, Virginia, Patient Representative
No conflicts noted.

Gary C. Yee, PharmD, University of Nebraska Medical Center, Omaha, NE
Pharmacology
Received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Novartis.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from American Society of Clinical Oncology, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

The following is available:

- Information for people living with cancer. Bisphosphonates for multiple myeloma. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2003 Feb. 12 p.

Electronic copies: Available in Portable Document Format (PDF) from the American Society for Clinical Oncology (ASCO) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on February 27, 2003. The information was verified by the guideline developer on March 14, 2003.

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